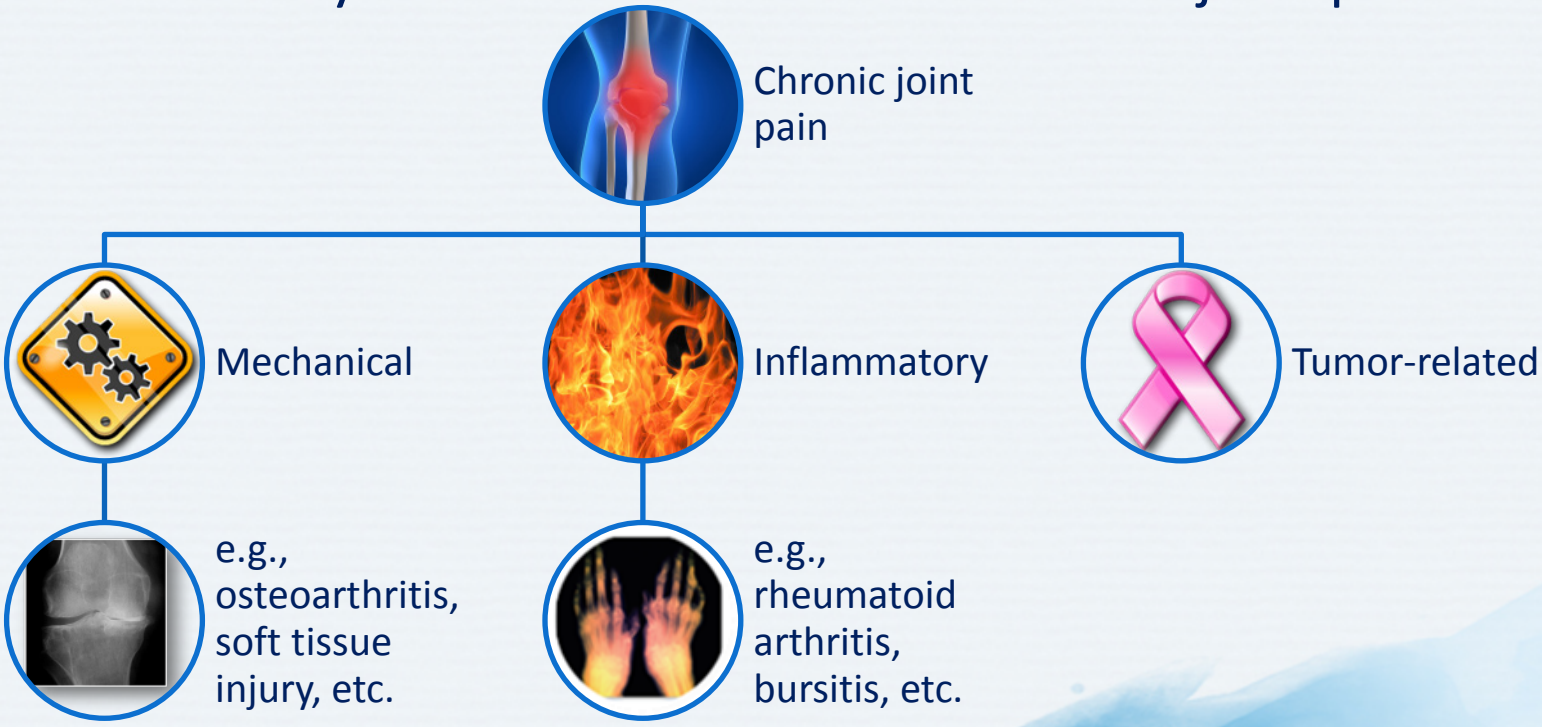
PATHOPHYSIOLOGY

Overview

What is chronic joint pain?

- Joint pain that persists beyond the normal expected tissue healing time of 3 months
- A wide variety of conditions can cause chronic joint pain



Davatchi F. In: Kopf A, Patel NB (eds). *Guide to Pain Management in Low-Resource Settings.* IASP Press; Seattle, WA: 2010; International Association for the Study of Pain. *Unrelieved Pain Is a Major Global Healthcare Problem.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Press_Release&Template=/CM/ContentDisplay.cfm&ContentID=2908. Accessed: July 19, 2013; Nielsen GP *et al. Semin Diagn Pathol* 2011; 28(1):37-52.

Etiology

Types of Joint Pain

Condition	Incidence per 100,000
Osteoarthritis	14,000
Rheumatoid arthritis	500–1000
Juvenile rheumatoid arthritis	100–200*
System lupus erythematosus	1–125
Polymyalgia rheumatica	5–60†
Giant cell arteritis	5–30
Ankylosing spondylitis	7

***In children**

†In individuals >50 years of age

Centers for Disease Control and Prevention. *Osteoarthritis*. Available at: http://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed: July 12, 2013;
Gabriel SE, Michaud K. *Arthritis Res Ther* 2009; 11(3):229.

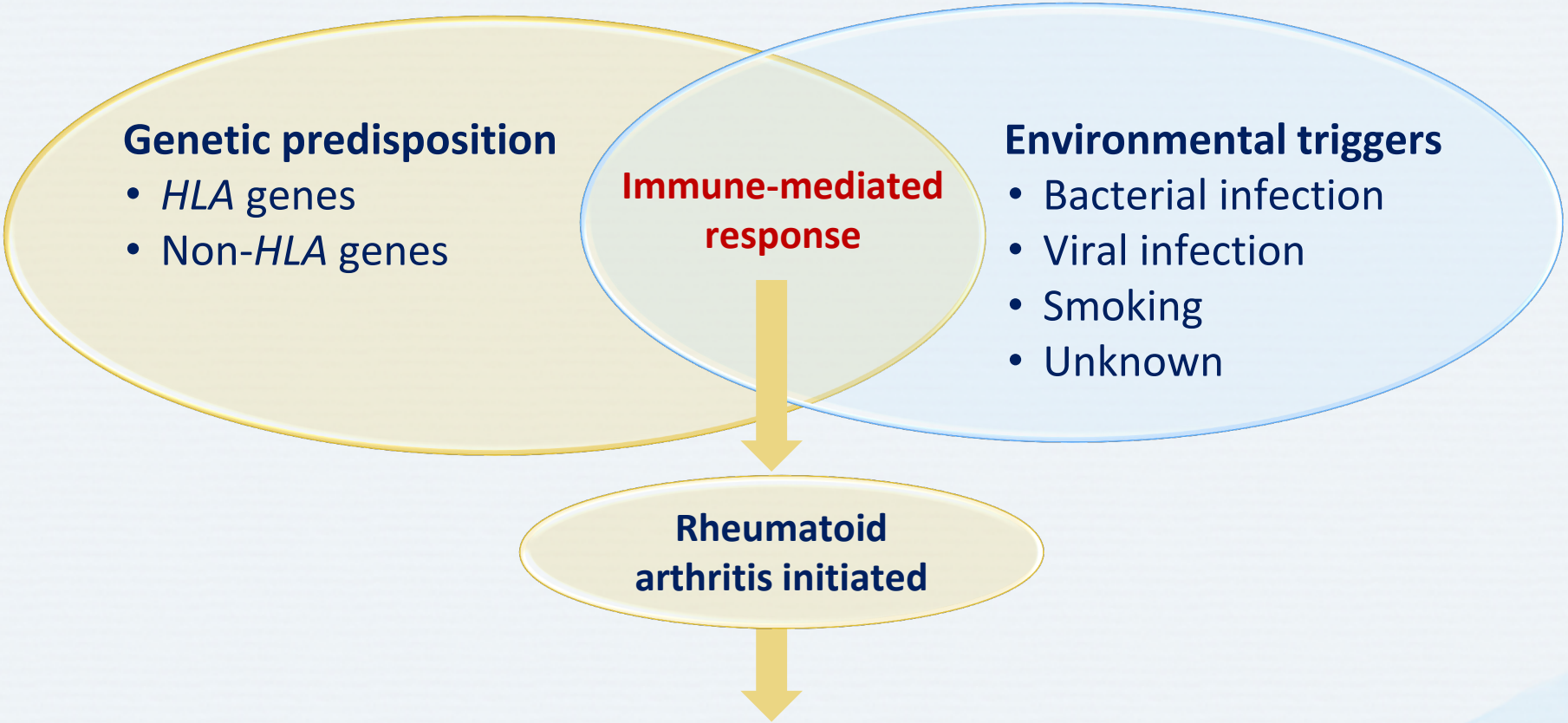
Ankylosing Spondylitis: Etiology

- Ankylosing spondylitis is a chronic inflammatory disease of unknown etiology
- It is considered an autoimmune disease
- HLA-B27 is the risk factor most often associated with ankylosing spondylitis
  - Mechanism of involvement is unclear
  - Subtypes and other features of the relationship between HLA-B27 and ankylosing spondylitis have been studied for years

HLA = human leukocyte antigen

Zambrano-Zaragoza JF *et al. Int J Inflam* 2013; 2013:501653.

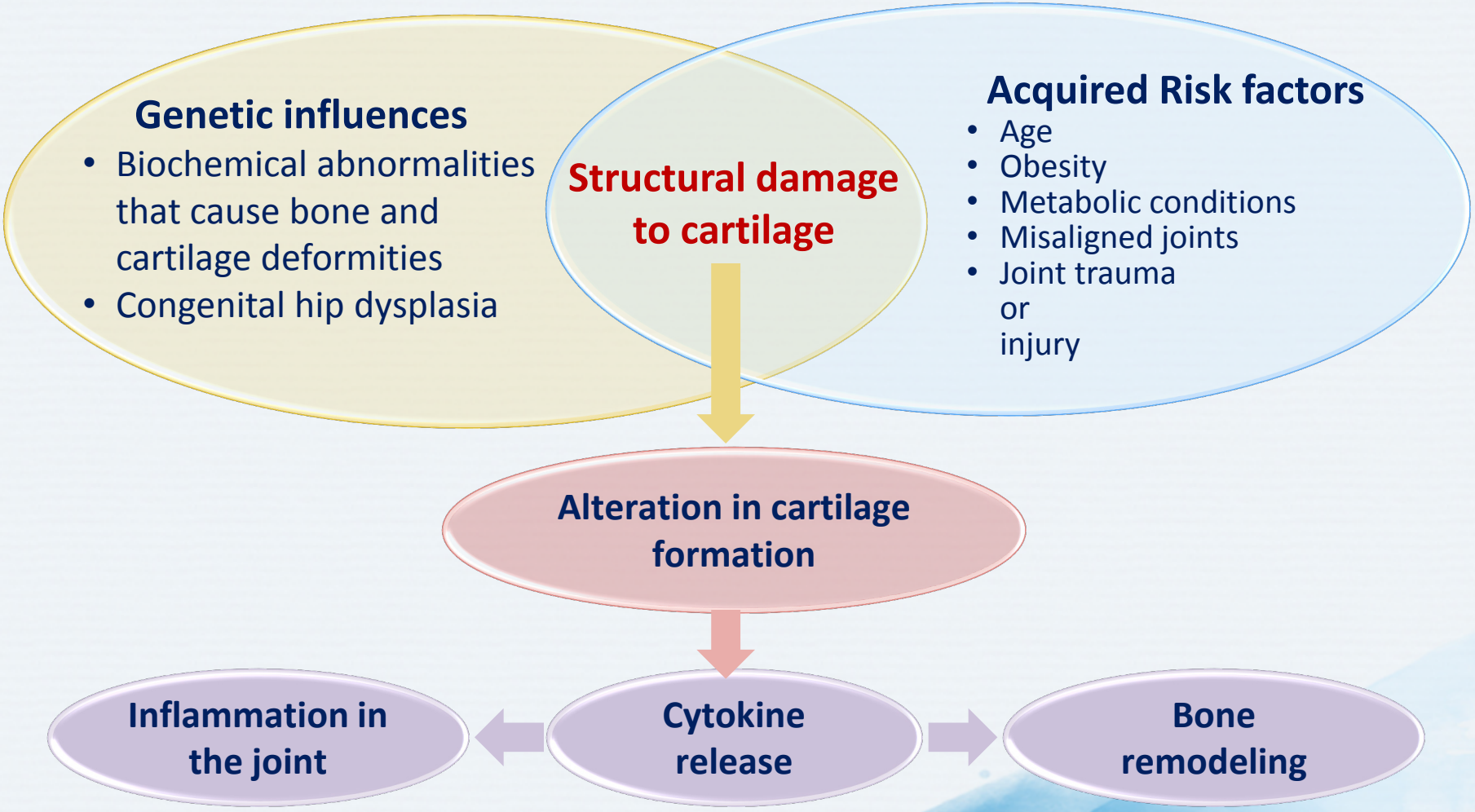
Rheumatoid Arthritis: Immune-Mediated Disease of Uncertain Etiology



HLA = human leukocyte antigen

O'Dell JR. In: Goldman L, Ausiello D (eds). *Cecil Medicine.* 23rd ed. Saunders Elsevier; Philadelphia, PA: 2007.

Osteoarthritis: Multifactorial Disease Etiology



Lane NE *et al*. In: Goldman L, Ausiello D (eds). *Cecil Medicine*. 23rd ed. Saunders Elsevier; Philadelphia, PA: 2007.

Pathophysiology

Ankylosing Spondylitis: Uncertain Etiology and Pathogenesis

- Incompletely understood, but knowledge is increasing[1]
- Immune-mediated mechanisms are involved[1]
  - Increased concentration of T cells, macrophages and proinflammatory cytokines
  - TNF-α is thought to play a role in the inflammatory reactions observed with the disease[2]
    - Inflammatory reactions produce hallmarks of disease[3,4]

Factors

- HLA-B27 – especially interaction between HLA-B27 and T cell response[1]
- Inflammatory cellular infiltrates
- Cytokines (e.g., TNF-α, IL-10)
- Genetics
- Environment

HLA = human leukocyte antigen; IL = interleukin; TNF = tumor necrosis factor

1. Sieper J *et al.* *Ann Rheum Dis* 2002; 61(Suppl 3):iii8-18; 2. Gorman JD *et al*. *N Engl J Med* 2002; 346(18):1349-56;
3. Khan MA. *Ann Intern Med* 2002; 136(12):896-907; 4. Khan MA. In: Hochberg MC *et al* (eds). *Rheumatology*. Vol 2, 3rd ed. Mosby; New York, NY: 2003.

Rheumatoid Arthritis Pathogenesis

Initiation*

↓

A. Immune response

↓

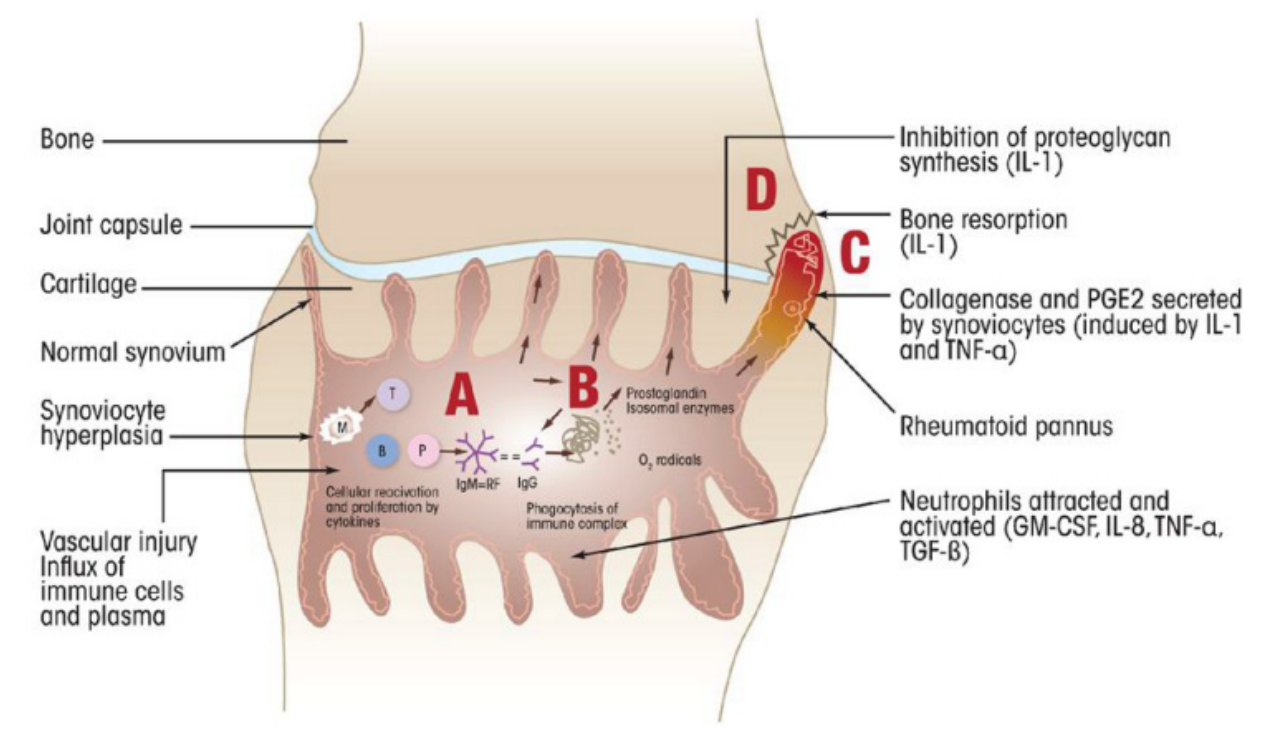
B. Inflammation

↓

C. Synovial overgrowth

↓

D. Joint destruction



***Initiation is typically attributed to a genetic predisposition or environmental trigger (not shown).**
B = B-lymphocyte; C = complement; GM-CSF = granulocyte-macrophage colony-stimulating factor; IgG = immunoglobulin G; IgM = immunoglobulin M; IL = interleukin; M = macrophage; P = plasma cell; PGE2 = prostaglandin E2; RF = rheumatoid factor; T = T-lymphocyte; TGF-β = transforming growth factor-β; TNF-α = tumour necrosis factor-α

O'Dell JR. In: Goldman L, Ausiello D (eds). *Cecil Medicine.* 23rd ed. Saunders Elsevier; Philadelphia, PA: 2007.

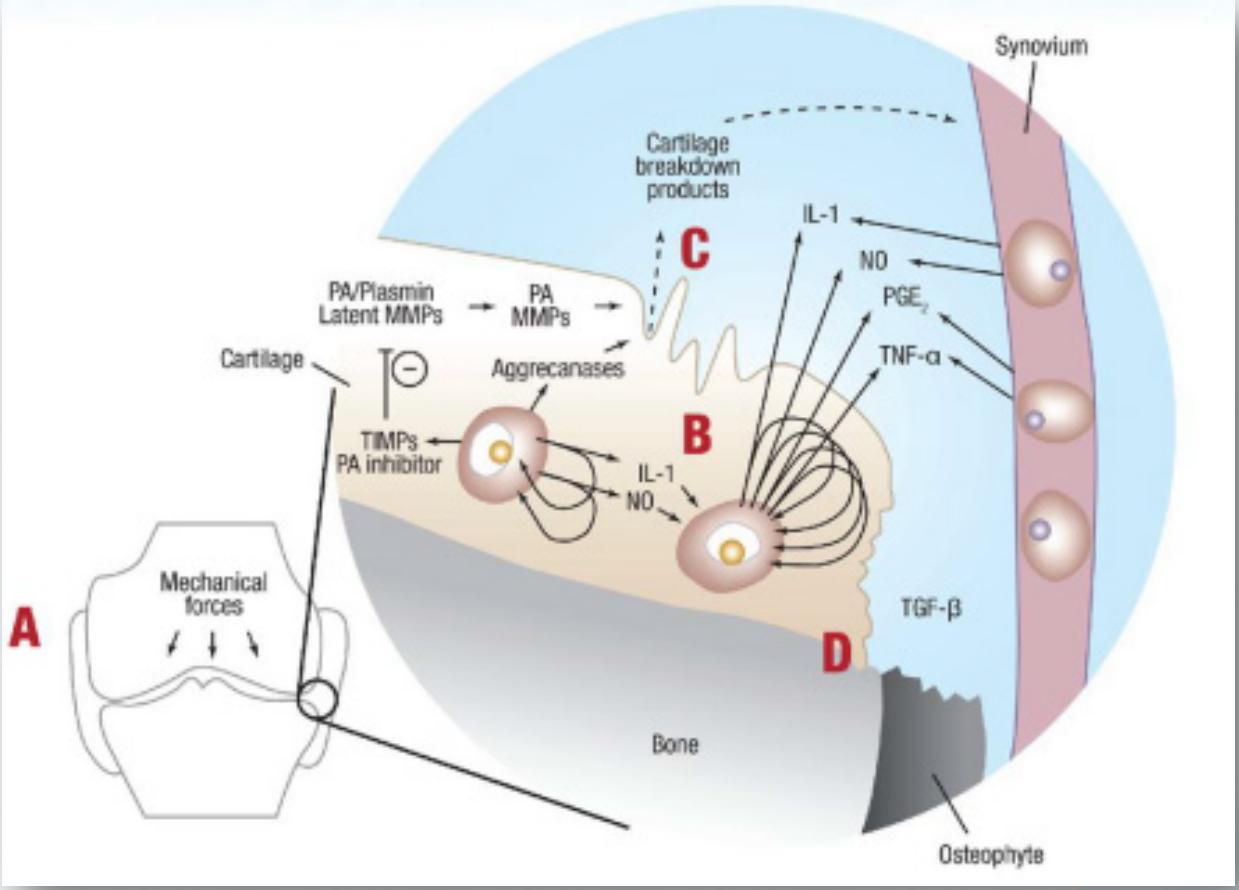
Osteoarthritis Pathogenesis

A. Mechanical stress

B. Inflammation

C. Cartilage breakdown

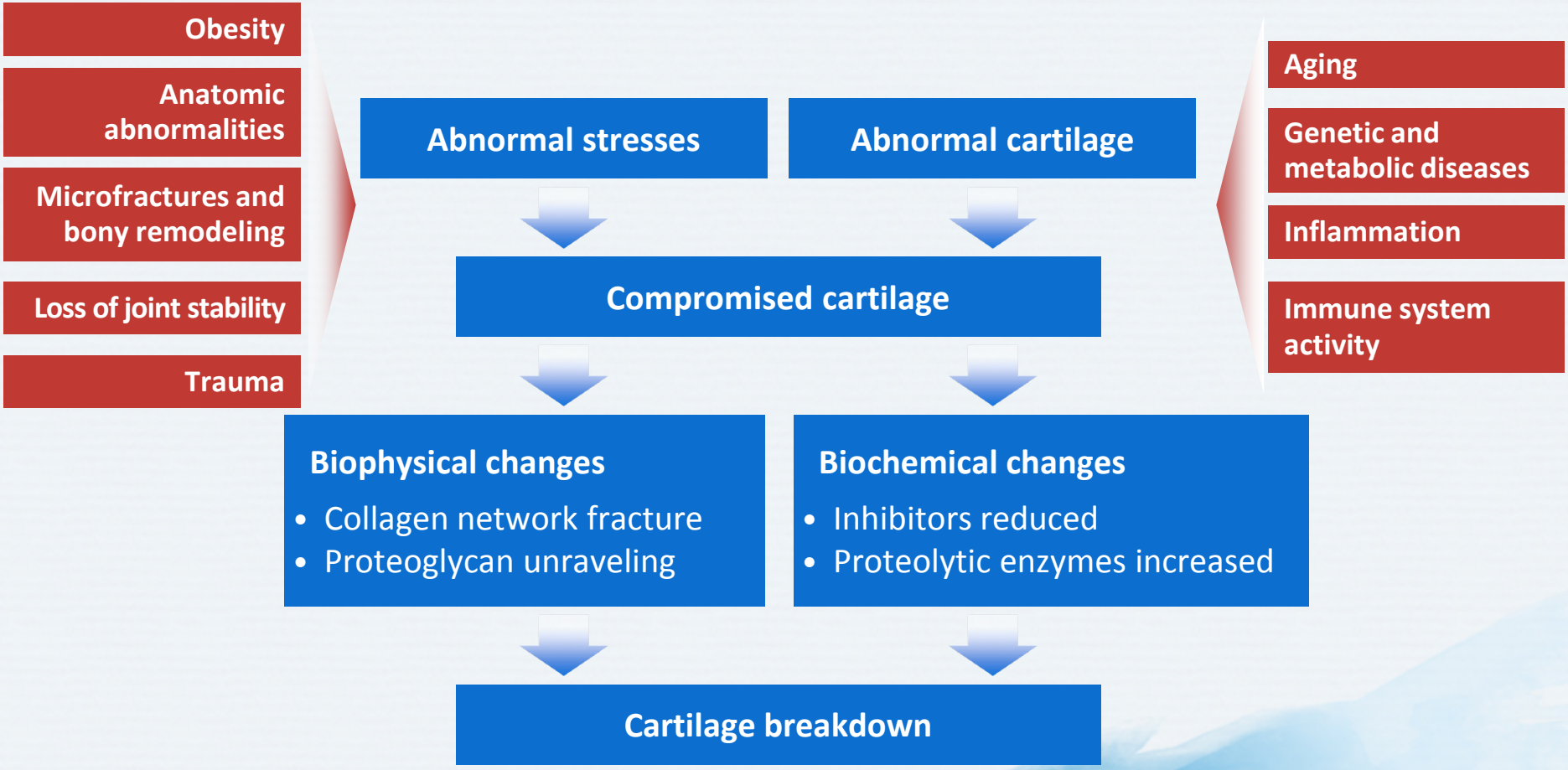
D. Joint damage



***Initiation is typically attributed to a genetic predisposition or environmental trigger (not shown).**
IL = interleukin; M = macrophage; MMP = metalloproteases; NO = nitric oxide; PGE2 = prostaglandin E2;
TGF-β = transforming growth factor-β; TIMP = tissue inhibitor of metalloproteases; TNF- α = tumor necrosis factor-α

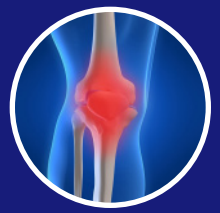
Firestein GS. In: Firestein GS *et al (eds). Kelley's Textbook of Rheumatology*. Vol 2, 8th ed. Saunders Elsevier, Philadelphia, PA; 2008;
Lane NE *et al*. In: Goldman L, Ausiello D (eds). *Cecil Medicine.* 23rd ed. Saunders Elsevier; Philadelphia, PA: 2007.

Factors Contributing to Osteoarthritis Development

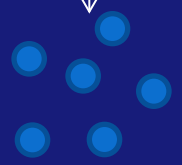


Mandelbaum B, Waddell D. *Orthopedics* 2005; 28(2 Suppl):S207-14.

Mechanism-Based Treatment of Inflammatory Pain



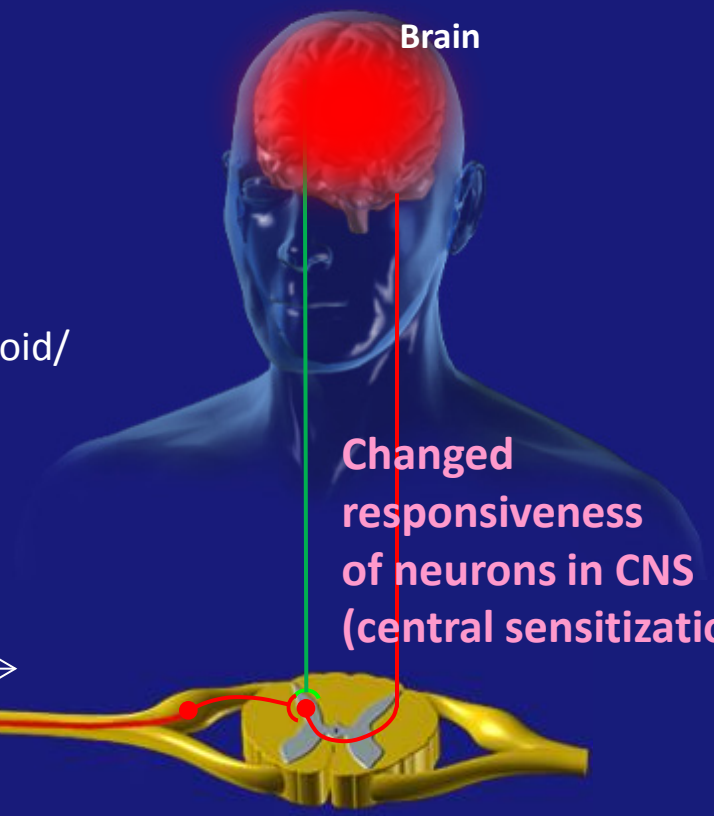
Damaged joint tissue



Inflammatory chemical mediators

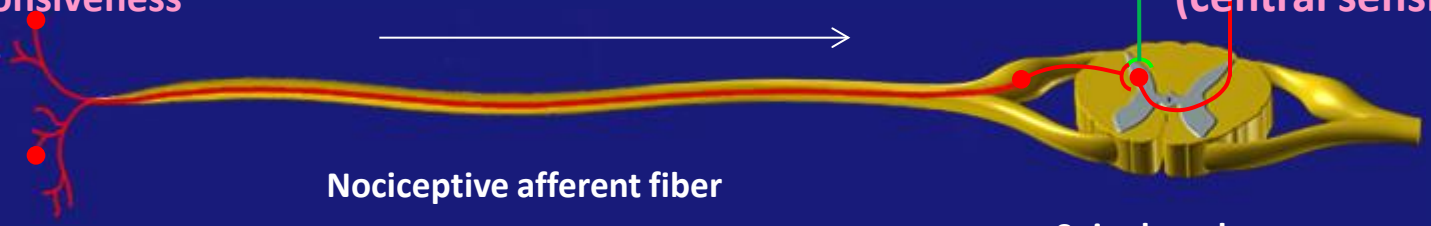
Pain Treatment Options

- Acetaminophen
- nNSAIDs/coxibs
- Opioids
- Local anesthetics/ channel blockers
- Intra-articular corticosteroid/ hyalurinate injections



Changed responsiveness of neurons in CNS (central sensitization)

Changed responsiveness of nociceptors (peripheral sensitization)



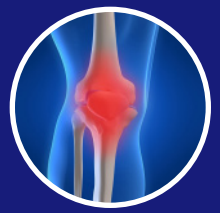
Nociceptive afferent fiber

Spinal cord

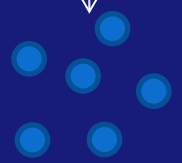
CNS = central nervous system; coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Hochberg MC *et al.* *Arthritis Care Res (Hoboken)* 2012; 64(4):465-74; Scholz J *et al*. *Nat Neurosci* 2002; 5(Suppl):1062-7.

Mechanism-Based Treatment of Chronic Pain in Osteoarthritis

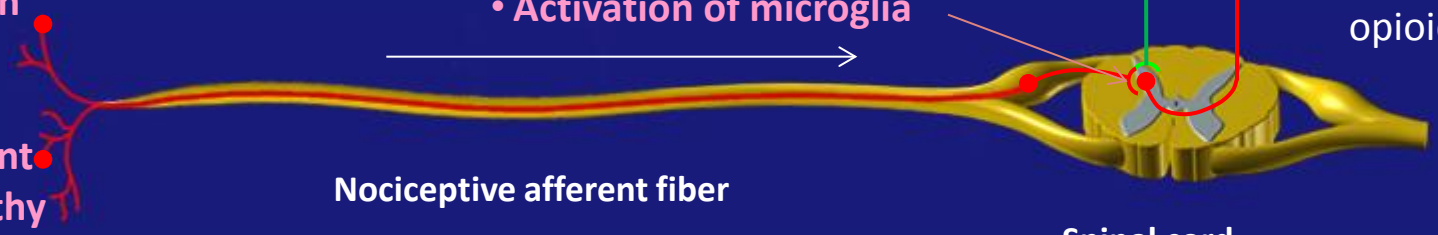


Damaged joint tissue



Inflammatory chemical mediators

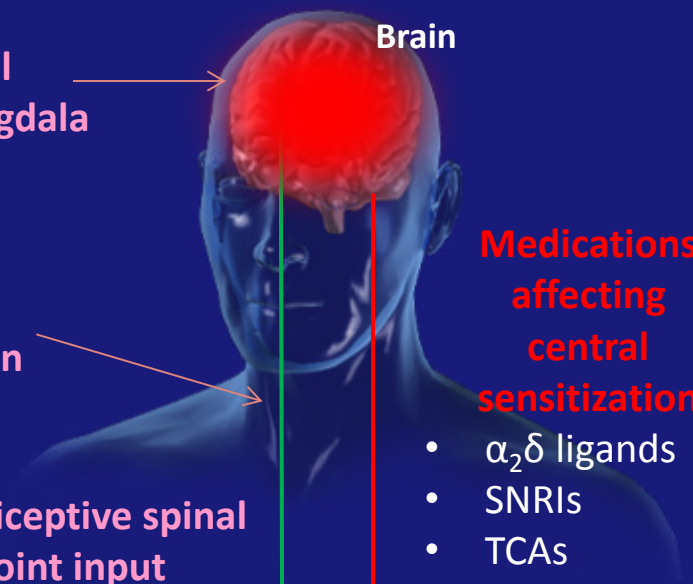
- Sensitization of joint nociceptors
- Development of neuropathy



Nociceptive afferent fiber

Spinal cord

- Activation of thalamocortical nociceptive system and amygdala
- Reduction of gray matter



Brain

- Changes in descending inhibition and facilitation
- Sensitization of nociceptive spinal cord neurons with joint input
- Activation of microglia

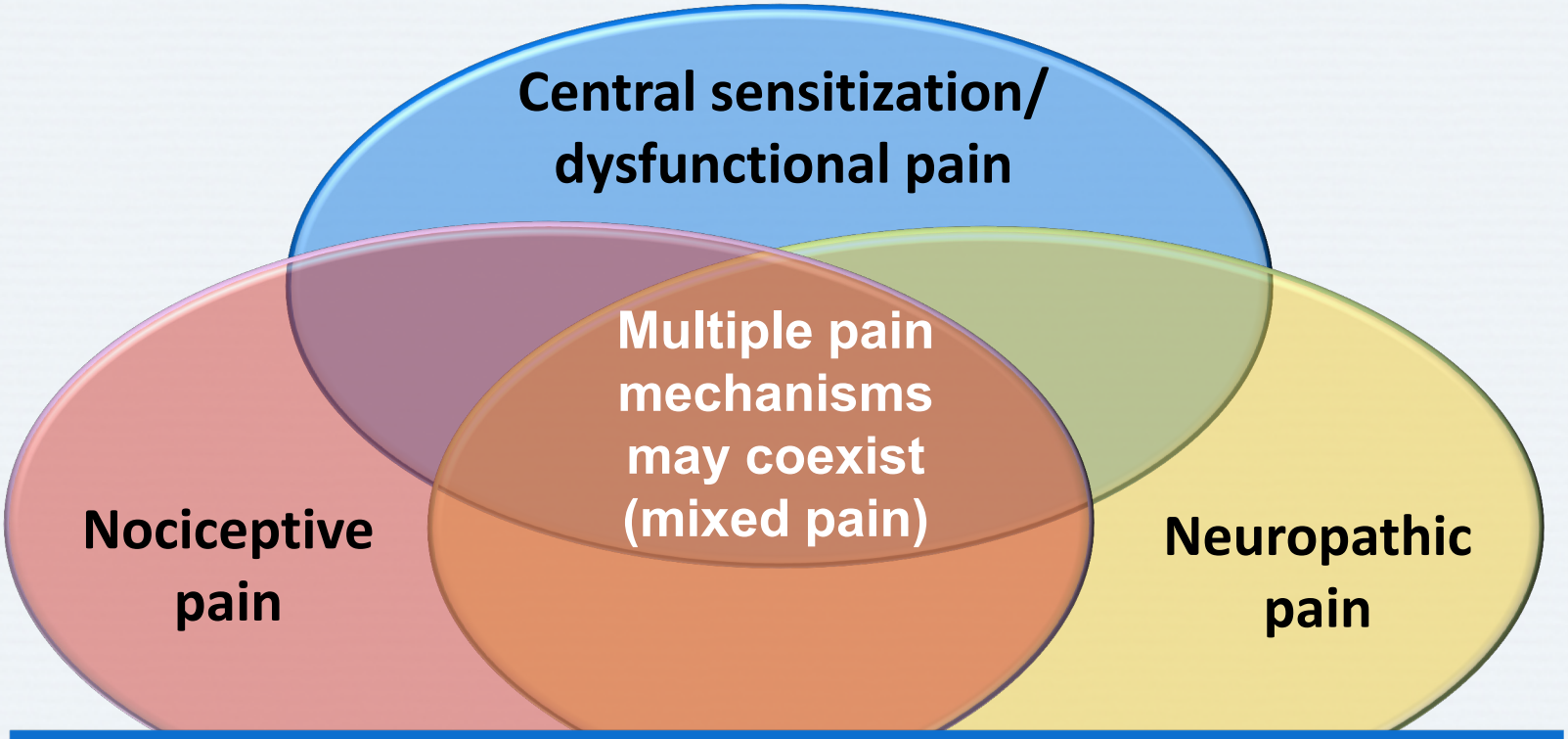
Medications affecting central sensitization

- $\alpha_2\delta$ ligands
- SNRIs
- TCAs
- Tramadol, opioids

CNS = central nervous system; coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Hochberg MC *et al.* *Arthritis Care Res (Hoboken)* 2012; 64(4):465-74; Scholz J *et al*. *Nat Neurosci* 2002; 5(Suppl):1062-7.

But… Patients with Chronic Pain of Just One Type of Pain Pathophysiology May be Rare



Therapies that work better for a particular patient are likely to depend on the mechanisms contributing to the patient's pain

Patients with mixed pain may benefit from ***combination therapy***

Otori S *et al. Yonsei Med J* 2012; 53(4):801-5; Vellucci R. *Clin Drug Investig* 2012; 32(Suppl 1):3-10.

Neuropathic Pain in Osteoarthritis

- Some osteoarthritis patients may use terms such as "burning" or "numbness" to describe their pain
  - These verbal descriptors are suggestive of a neuropathic component
- Based on mechanism of action and preliminary studies, non-traditional analgesics such as $\alpha_2\delta$ ligands, TCAs and SNRIs, may be useful for treating this component
  - However, further studies are needed to clarify the role of these drugs in osteoarthritis

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

Mease PJ *et al. J Rheumatol* 2011; 38(8):1546-51.

Neuropathic Pain in Osteoarthritis

- The exact cause of osteoarthritis pain remains unclear
  - Pathological changes in articular structures
  - Changes in central pain processing or central sensitization appear to be involved[1]
- Some osteoarthritis patients may use terms such as “burning” or “numbness” to describe their pain [2]
  - These verbal descriptors suggest a neuropathic component
- Based on mechanism of action and preliminary studies, non-traditional analgesics (*e.g.*, $\alpha_2\delta$ ligands, TCAs, SNRIs) may be useful for treating this component
  - Further studies are needed to clarify the role of these drugs in osteoarthritis

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

1. Girbés Ll. Phys Ther. 2013 Jun;93(6):842-51
2. Mease PJ *et al. J Rheumatol* 2011; 38(8):1546-51.

Central Sensitization in Osteoarthritis

- Central sensitization may contribute to osteoarthritis pain in a subgroup of patients (~30%)
  - Hypothesis supported by a variety of direct and indirect evidence
- Several interventions (including manual therapy, TENS, medication and joint replacement surgery) have been shown to modulate central hyperexcitability, but more research is required

TENS = transcutaneous electrical nerve stimulation

Lluch E *et al. Eur J Pain* 2014; [Epub ahead of print].

Summary

Pathophysiology of Chronic Joint Pain: Summary

- Chronic joint pain can be due to many causes: mechanical, inflammatory or tumor-related
- Many conditions associated with chronic joint pain are complex, multifactorial disease
  - Some conditions, such as rheumatoid arthritis and ankylosing spondylosis, involve immune-mediated mechanisms
  - Others, like osteoarthritis, are primarily due to mechanical stress and cartilage breakdown
  - Many conditions associated with chronic joint pain are complex, multifactorial disease
- Chronic joint pain due to arthritis is frequently inflammatory in nature
  - However, many patients with osteoarthritis and rheumatoid arthritis may also have a neuropathic component to their pain